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Evidence for a Common Etiology for Endometrial Carcinomas and Malignant Mixed Mullerian Tumors

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Objective. **To elucidate factors linked to the development of malignant mixed mullerian tumors (MMMT) and determine whether the risk factor profile for these tumors corresponds with that for the more common endometrial carcinomas.**

Methods. **A multicenter case–control study of 424 women diagnosed with endometrial carcinoma, 29 women diagnosed with MMMT, and 320 community controls was conducted. Review of pathological reports and slides was performed to classify cases by histological type. All participants were asked to respond to a questionnaire which ascertained information on exposure to factors postulated to be linked to the development of uterine tumors.**

Results. **Women with endometrial carcinomas and MMMTs were similar with respect to age and educational attainment. Women diagnosed with MMMTs were more likely than those diagnosed with carcinomas to be of African–American descent (28% vs 4%; $P = 0.001$). Weight, exogenous estrogen use, and nulliparity were related to risk of both tumor types. Marked obesity was associated with a 4.8-fold (95% CI = 3.0,7.6) increase in risk of carcinoma and a 3.2-fold (95% CI = 1.1,9.1) increase in risk of MMMT development. Use of exogenous estrogens increased the odds of developing carcinomas by 2-fold (95% CI = 1.3,3.2) and that of developing MMMTs by 1.8-fold (95% CI = 0.57,5.5). Nulliparity was associated with a 2.9-fold (95% CI = 1.9,4.8) increase in risk of carcinomas and a 1.7-fold (95% CI = 0.53,5.6) increase in risk of MMMTs. Oral contraceptive use protected against the development of both carcinomas (OR = 0.39; 95% CI = 0.26,0.58) and MMMTs (OR = 0.76; 95% CI = 0.25,2.3). Current smokers were at a reduced risk of developing endometrial carcinomas (OR = 0.34; 95% CI = 0.21,0.55) and MMMTs (OR = 0.57; 95% CI = 0.15,2.3), while former smokers were at an increased risk of MMMT (OR = 2.7; 95% CI = 1.1,6.8) but not carcinoma development (OR = 0.81; 95% CI = 0.56,1.2).**

Conclusion. **Results from this study suggest that MMMTs and carcinomas have a similar risk factor profile. This observation is compatible with the hypothesis that the pathogenesis of these two histological types of uterine tumors is similar.**

INTRODUCTION

Malignant tumors of the uterine corpus are broadly divisible into three main types: carcinomas, sarcomas, and carcinosarcomas or malignant mixed mullerian tumors (MMMTs). Because endometrial carcinomas are vastly more common than other uterine tumors, the epidemiology of these neoplasms has been studied more extensively [1–6]. Although sarcomas and MMMTs are rare, delineating the etiology of these neoplasms is of interest because they have the tendency to behave more aggressively than carcinomas and contribute to a disproportionate number of uterine cancer deaths.

Endometrial carcinogenesis is strongly associated with risk factors believed to be linked to excess estrogen exposure such as obesity and long-term estrogen use [1–6]. The association between these exposures and the development of MMMTs has not been extensively studied. Results from the single epidemiological study which has examined MMMTs as a separate entity from other uterine sarcomas suggested a role of estrogen use in the pathogenesis of MMMTs, similar to that observed for endometrial carcinomas [7, 8]. Understanding the pathogenesis of MMMTs is especially important because the classification of these tumors has been in flux. Historically, MMMTs were grouped with sarcomas [9, 10], but accumulating clinical and pathological evidence suggests that these tumors represent carcinomas that have undergone clonal evolution, resulting in the acquisition of sarcomatous features [11–17].

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The prognosis of MMMTs, in which the epithelial component generally resembles an aggressive subtype of endometrial carcinoma, tends to be poor irrespective of the appearance of the sarcomatous elements [16]. Histologically, early metastases of MMMTs are usually composed exclusively of carcinomatous elements [11, 16]. Well-documented metastases displaying sarcomatous differentiation have been identified most frequently at autopsy or in patients with widely disseminated metastatic disease [18, 19]. Ultrastructural studies of MMMTs have demonstrated that these tumors may contain hybrid cells with both epithelial and mesenchymal characteristics [12]. Similarly, the sarcomatous elements often express epithelial markers such as keratin when examined immunohistochemically [11, 17]. In addition, both the carcinomatous and sarcomatous elements usually show similar expression of immunohistochemical markers, including p53 protein [20, 21]. Cytogenetic and immunohistochemical studies performed on cell cultures also suggest that MMMTs represent monoclonal rather than biclonal tumors [13–15]. In short, clinical, pathologic, and biologic investigations suggest that MMMTs are monoclonal tumors which are biologically related to carcinomas, but epidemiologic data to support this viewpoint are sparse.

To examine the association between putative endometrial cancer risk factors and MMMTs, we analyzed the results from a case–control study which included diverse types of malignant endometrial tumors. We hypothesized that the risk factor profile for endometrial carcinomas and MMMTs would be similar.

METHODS

Selection of Cases and Controls

Cases were selected from a multi-institutional, case–control study of 498 incident endometrial cancers sponsored by the National Cancer Institute. This study is described in detail elsewhere [1]. Subjects between 20 and 74 years of age residing in the catchment areas served by the five participating institutions were eligible. Patients were recruited prior to treatment over a 36-month interval.

A total of 481 population-based controls individually matched to cases on age (5-year groups), race, and residential area were identified. For women younger than 65 years of age, random digit dialing techniques were used to select controls. Health Care Financing Administration files were used to choose controls for cases 65 years of age or older.

Pathology

Pathology reports were available for 481 (96.6%) of the 498 cases. Diagnostic classification was based largely on review of pathology reports. In the few instances (<10% of cases) where report review was inconclusive or conflicting, microscopic reexamination of the histologic slides was performed by the study pathologist (MES). The final classification of the tumors was carcinoma in 424 cases and MMMT in 29; 26 cases classified as pure sarcomas of various subtypes, 2 cases with uncertain histology, and 17 cases with no pathology reports or slides available for review were considered ineligible for the present study and were excluded from the analysis.

Ascertainment of Risk Factor Data

Home interviews were performed on 404 (89.2%) of eligible cases and 320 (66.5%) of eligible controls by trained interviewers. The interviews obtained information on a variety of factors possibly related to endometrial cancer risk, including menstrual and obstetric history, use of exogenous estrogens and oral contraceptives, and smoking history.

Analysis

Differences between means were compared using Student's *t* test [22]. Contingency table analyses were performed to compare study groups with respect to the distribution of established risk factors and the χ^2 test was used to determine significance of findings [22]. Logistic regression analysis was used to estimate odds ratios (OR) associated with particular exposures [23]. Significance testing was performed by examining 95% confidence intervals of estimates. To assure that only women with the potential for the exposure of interest were investigated, analysis of estrogen use was limited to women over 40 years of age, and oral contraceptive use was examined only in women under 70 years of age.

RESULTS

Patient Characteristics

MMMTs tended to be diagnosed at more advanced stages than carcinomas, with 27% of MMMTs, but only 9% of carcinomas being stages III/IV at diagnosis ($P = 0.004$). Fifty-nine percent of cases with MMMTs were diagnosed with stage I disease compared to 77% of women with carcinomas. Demographic characteristics of the women in this study are presented in Table 1 according to histologic tumor type. Women with carcinomas and MMMTs were similar in age (median age = 62.8 years for MMMTs and 61 years for carcinomas; $P = 0.15$). A disproportionate number of women with a diagnosis of MMMT were of African–American descent (28% compared to 4% of women diagnosed with carcinomas; $P = 0.001$) . Educational levels were similar in the two groups ($P = 0.70$).

Cancer Risk Factors

Risk factors for endometrial cancer in this population have been previously reported [1, 24–26]. As shown in Table 2, these data confirm that marked obesity, exogenous estrogen use and nulliparity are associated with increased risk of endometrial carcinomas. Smoking and oral contraceptive use were associated with decreased risk. Apart from smoking, the directionality of the associations between the exposures studied and tumor development were the same for MMMTs as for carcinomas.

Marked obesity was associated with an age- and race-adjusted 4.8-fold (95% CI = 3.0, 7.6) and 3.2-fold (95% CI = 1.1, 9.1)

TABLE 1
Demographic Features of Women with Endometrial Carcinoma and MMMTs

	Carcinomas (n = 424)	Mixed mullerian tumors (n = 29)
Age at diagnosis		
Range, in years	25–74	31–74
Median age	61 years	62.8 years
Mean age	59.1 years	61.3 years
	$P = 0.15$[a]	
% Caucasian	82%	62%
% Black	4%	28%
% Other	14%	10%
	$P = 0.001$[c]	
Education[b]		
% < College	68%	72%
% College	32%	28%
	$P = 0.70$[c]	

[a] P value comparing mean age of the two case groups, using the t test.
[b] Four mixed mullerian tumor cases and 52 carcinomas with unknown educational level excluded.
[c] P value comparing distribution of the two case groups using the Pearson χ^2 test.

increase in risk of developing carcinomas and MMMTs, respectively. Women exposed to exogenous estrogen were at excess risk for both histological types of tumors. The age and race adjusted OR estimates for carcinomas and MMMTs were 2.0 (95% CI = 1.3, 3.2) and 1.8 (95% CI = 0.57, 5.5), respectively. Long-term use (defined as >10 years of use) was associated with age and race adjusted ORs of 6.5 for carcinomas (95% CI = 2.5, 17) and 6.6 for MMMTs (95% CI = 1.1, 38). Nulliparity conferred a 2.9-fold increase in risk of developing carcinomas (95% CI = 1.9, 4.8) and a nonsignificant 1.7-fold increase in risk of developing MMMTs (95% CI = 0.53, 5.6).

Oral contraceptive use was associated with a decreased risk for both types of tumors. The protective effect appeared stronger for carcinomas (age and race adjusted OR = 0.39; 95% CI = 0.26, 0.58) than for MMMTs (age and race adjusted OR = 0.76; 95% CI = 0.25, 2.3). No evidence of increasing protection with increasing years of oral contraceptive use was observed for either tumor type, when short-term (defined as <5 years) and long-term (defined as 5+ years) users were examined (data not shown). Compared with women who had never smoked, current users were at a reduced risk for both tumor types. The age- and race-adjusted OR estimates for carcinomas and MMMTs were 0.34 (95% CI = 0.21, 0.55) and 0.57 (95% CI = 0.15, 2.3), respectively. Former users were at increased risk of MMMTs (age and race adjusted OR = 2.7; 95% CI = 1.1, 6.8).

TABLE 2
Distribution and Risk Associated with Selected Risk Factors among Uterine Cancer Cases by Histological Type

Factor	Controls, n (n = 320)	Carcinomas (n = 378)			Mixed mullerian tumors (n = 26)		
		n	%	OR[a] (95% CI)	n	%	OR[a] (95% CI)
Weight[b]							
<200 lbs	290	262	70	1.0	19	73%	1.0
≥200 lbs	29	111	30	4.8 (3.0,7.6)	7	27%	3.2 (1.1,9.1)
Exogenous estrogen use[c]							
Never	268	281	79	1.0	19	79%	1.0
Ever	33	74	21	2.0 (1.3,3.2)	5	21%	1.8 (0.57,5.5)
Parity							
Parous	291	293	78	1.0	22	85%	1.0
Nulliparous	29	85	22	2.9 (1.9,4.8)	4	15%	1.7 (0.53,5.6)
Oral contraceptive use[d]							
Never	167	251	78	1.0	17	71%	1.0
Ever	114	72	22	0.39 (0.26,0.58)	7	29%	0.76 (0.25,2.3)
Cigarette smoking[e]							
Never	182	257	69	1.0	12	46%	1.0
Former	75	85	22	0.81 (0.56,1.2)	11	42%	2.7 (1.1,6.8)
Current	63	30	8	0.34 (0.21,0.55)	3	12%	0.57 (0.15,2.3)

[a] Adjusted for age and race.
[b] Six women with unknown weight excluded.
[c] Restricted to women 40 years of age or older. Ten women with unknown estrogen status excluded.
[d] Restricted to women under the age of 70.
[e] Six women with unknown smoking status excluded.

DISCUSSION

This study demonstrates that the risk factors for MMMTs and endometrial carcinomas are generally similar. Our data suggest that marked obesity, exogenous estrogen use, and nulliparity appear to increase risk for the development of both types of neoplasms. These findings are similar to previously reported data indicating that obesity and long-term or recent exogenous estrogen use are linked to an increased risk of developing MMMT [7]. Although nulliparity was associated with a modest increase in risk for the development of MMMTs in our study, the risk appeared to be less than that observed for carcinomas. In a previous study, parity was unrelated to risk of MMMTs [8].

Oral contraceptive use and cigarette smoking were associated with a decreased risk of developing endometrial carcinoma in the current report and previous studies [24, 25, 27]. Our results suggest that oral contraceptive use and cigarette smoking were also associated with a decreased risk for developing an MMMT; however, the effects appeared weaker. Paradoxically, while current smokers were at a reduced risk for MMMTs (OR = 0.57), former smokers were at a significantly increased risk for MMMTs (OR = 2.7). The implications of this observation are unclear and could reflect a chance finding. Although the apparent protective effect of smoking in endometrial carcinoma has been attributed to increased catabolism or binding of estrogens, this effect has never been proven [28]. The possibility that the relationship between smoking and endometrial cancer risk is unrelated to estrogen metabolism is plausible because smoking has myriad pathophysiologic effects, including modulation of p450 enzymes which has many biochemical consequences.

Endometrial carcinomas and MMMTs also differed in another respect: 28% of women with MMMTs were African–American compared with 4% of patients with carcinomas [29]. Whether this result reflects differences in environmental exposures, genetic factors, biased selection of cases, chance, or perhaps multiple factors is unknown.

Recent developments in our understanding of the etiology of histological subtypes of endometrial carcinomas may have important implications for our understanding of the etiology of MMMTs as well. These studies suggest that risk factors for endometrial carcinoma differ by histologic subtype [30]. Recognized endometrial cancer risk factors reflecting excess estrogen exposure, such as obesity and menopausal estrogen use, are strongly linked to the development of endometrioid carcinomas, but the development of other tumor types, such as serous carcinoma, may be weakly related or unrelated to these factors. Although serous carcinomas account for less than 10% of endometrial carcinomas, MMMTs in which the epithelial component displays serous differentiation may be slightly overrepresented. In fact, of the 29 MMMTs in the current study, 5 (17%) were found to display serous differentiation. Given that MMMTs may develop from preexisting carcinomas, a larger study in which the epidemiology of MMMTs are stratified based on the appearance of the carcinomatous elements would be of interest.

The conclusions of this study are limited by the small number of MMMTs available for evaluation. Despite this limitation, the present study provides a risk factor analysis using data collected from cases and internal controls diagnosed in diverse regions of the United States, with expert pathology review. In addition, the present study recruited incident cases prior to treatment, thus avoiding potential biases which might be encountered in studies in which a significant number of cases are deceased.

In conclusion, this study demonstrates that risk factors for MMMTs and carcinomas are generally similar. This finding is compatible with the hypothesis that the pathogenesis of MMMTs and carcinomas is similar, and that MMMTs represent carcinomas which have secondarily developed sarcomatous differentiation. Confirmation of these findings in larger studies is needed.

REFERENCES

1. Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, Lannom L, Hoover RN: Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case–control study. Am J Obstet Gynecol 167: 1317–1325, 1996
2. Cole P, Rothman KJ, Kaplan SD: Epidemiology of endometrial cancer. J Natl Cancer Inst 59: 1055–1060, 1977
3. Henderson BE, Casagrande JT, Pike MC: The epidemiology of endometrial cancer in young women. Br J Cancer 47: 749–756, 1983
4. Kelsey JL, LiVolsi VA, Holford TR, Fischer DB, Mostow ED, Schwartz PE, O'Connor T, White C: A case–control study of cancer of the endometrium. Am J Epidemiol 116: 333–342, 1982
5. La Vecchia C, Francheschi S, Decarli A, Gallus G, Tognoni, G: Risk factors for endometrial cancer at different ages. J Natl Cancer Inst 73: 667–671, 1984
6. Wynder EL, Escher GC, Mantel N: An epidemiological investigation of cancer of the endometrium. Cancer 19: 489–520, 1966
7. Schwartz SM, Weiss NS, Daling JR, Gammon MD, Liff JM, Watt J, Lynch CF, Newcomb PA, Armstrong BK, Thompson WD: Exogenous sex hormone use, correlates of endogenous hormone levels, and the incidence of histologic types of sarcoma of the uterus. Cancer 77: 717–724, 1996
8. Schwartz, S.M., Weiss, N.S., Daling, J.R., Newcomb, P.A., Liff, J.M., Gammon, M.D., Thompson, W.D., Watt, J.D., Armstrong, B.K., Weyer, P.I., P., and Ek, M: Incidence of histologic types of uterine sarcoma in relation to menstrual and reproductive history. Int J Cancer 49: 362–367, 1991
9. Kvale G, Heuch I, Ursin, G: Reproductive factors and risk of cancer of the uterine corpus: a prospective study. Cancer Res 48: 6217–6221, 1988
10. Schwartz SM, Thomas DB, The World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives: A case–control study of risk factors for sarcomas of the uterus. Cancer 64: 2487–2492, 1989
11. Bitterman P, Chun B, Kurman RJ: The significance of epithelial differentiation in mixed mesodermal tumors of the uterus. Am J Surg Pathol 14: 317–328, 1990
12. De Brito PA, Silverberg SG, Orenstein JM: Carcinosarcoma (malignant mixed mullerian mesodermal) tumor of the female genital tract: Hum Pathol 24: 132–142, 1993

13. Emoto M, Iwasaki H, Kikuchi M, Ishiguro M, Kubota T, Izumi H, Shirakawa K, Yasuhiko K: Two cell lines established from mixed mullerian tumors of the uterus. Cancer 69: 1759–1768, 1992
14. Emoto M, Iwasaki H, Kikuchi M, Shirakawa K: Characteristics of cloned cells of mixed mullerian tumor of the human uterus: carcinoma cells showing myogenic differentiation in vitro. Cancer 71: 3065–3075, 1993
15. Gorai I, Doi C, Minaguchi H: Establishment and characterization of carcinosarcoma cell line of the human uterus. Cancer, 71: 775–86, 1993
16. Silverberg SG, Major FJ, Blessing JA, Fetter B, Askin FB, Liao SY, Miller A: Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. Intl J Gynecol Pathol 9: 1–19, 1990
17. Sreenan JJ, Hart WR: Carcinosarcomas of the female genital tract. Am J Surg Pathol 19: 666–674, 1995
18. Doss LL, Llorens AS, Henriques EM: Carcinosarcoma of the uterus: a 40-year experience from the state of Missouri. Gynecol Oncol 18: 43–53, 1984
19. Deligdisch L, Plaxe S, Cohen CJ: Extrauterine pelvic malignant mixed mesodermal tumors: a study of 10 cases with immunohistochemistry. Int J Gynecol Pathol 7: 361–72, 1988
20. Costa JJ, Vogelsang J, Young LJT: p53 gene mutation in female genital tract carcinosarcomas (malignant mixed mullerian tumors): a clinicopathologic study of 74 cases. Mod Pathol 7(61994)
21. Sherman ME, Bur M, Kurman RJ: P53 in endometrial cancer and its putative precursors: evidence for diverse pathways of tumorigenesis. Hum Pathol 26: 1268–1274, 1995
22. Dixon WJ, Massey FJ: Introduction to Statistical Analysis. New York, McGraw–Hill, 1983
23. Breslow NE, Day NE: Statistical Methods in Cancer Research: The Analysis of Case–Control Studies. IARC Publ No 32, 1980
24. Brinton LA, Barrett JJ, Berman ML, Mortel R, Twiggs LB, Wilbanks GD: Cigarette smoking and the risk of endometrial cancer. Am J Epidemiol 137: 281–291, 1993
25. Brinton LA, Hoover RN: Estrogen replacement therapy and endometrial cancer risk: unresolved issues. Obstet Gynecol 81: 265–271, 1993
26. Potischman N, Hoover RN, Brinton LA, Siiteri P, Dorgan JF, Swanson CA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, Persky V, Lurain JR:. A case–control study of endogenous steroid hormones and endometrial cancer. J Natl Cancer Inst 88: 1127–1135, 1996
27. Cancer and Steroid Hormone (CASH) Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Combination oral contraceptive use and the risk of endometrial cancer. JAMA 257: 796–800, 1987
28. Meredith RF, Eisert DR, Kaka Z, Hodgson SE, Johnston GA, Boutselis JG: An excess of uterine sarcomas after pelvic irradiation. Cancer 58: 2003–2007, 1986
29. Harlow BL, Weiss NS, Lofton S: The epidemiology of sarcomas of the uterus. J Natl Cancer Inst 76: 399–402, 1986
30. Sherman ME, Sturgeon S, Brinton LA, Potischman N, Kurman RJ, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD: Epidemiologic evidence for and estrogen independent pathway of endometrial carcinogenesis: a case–control study of endometrioid and serous carcinoma. Submitted for publication